example, at page 6, line 25 through page 7, line 11; page 8, line 20 through page 9, line 2; page 10, line 27 through page 11, line 14; SEQ ID NO:1 and SEQ ID NO:2. A typographical error at page 13, line 6, of the specification has been corrected to properly reflect that DSP-14, an abbreviation repeated throughout the application, is an abbreviation for "dual specificity phosphatase-14" and not for "dual specificity phosphatase-6." No new subject matter has been added.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

OBJECTION TO THE CLAIMS

The Examiner objected to claim 6 for informality because claim 6 depends from non-elected claim 1.

Applicants thank the Examiner for pointing out the informality of the pending claim, and submit that as amended the instant claim no longer recites improper dependency on non-elected claim 1. Applicants therefore submit that claim 6 is now in proper form and respectfully request that the Examiner withdraw the objection.

REJECTION UNDER 35 U.S.C. § 101 AND 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 2-14 under 35 U.S.C. § 101, asserting that the claimed invention has no credible, specific, or substantial utility. More specifically, the Examiner asserts that the invention has no credible utility because allegedly other polynucleotides with homologous sequences encode polypeptides with different utility and function, such as a phospholipase taught by Acton (U.S. Patent No. 6,268,135), a protein tyrosine phosphatase disclosed in Acton (U.S. Patent No. 6,258,582), and a phosphatase SEQ ID NO:4 disclosed in Bandman et al. (U.S. Patent No. 6,132,964). The Examiner further asserts that the specification does not disclose a specific function of the DSP-14 polypeptide or its relationship to a disease that would support a specific real world use for the claimed invention. The Examiner also rejected claims 2-14 under 35 U.S.C. § 112, first paragraph, for lack of enablement. In particular, the Examiner asserts that because the claimed invention allegedly has neither a

specific, substantial, and credible utility nor a well-established utility, one skilled in the art would not know how to make and use the claimed invention.

Applicants respectfully traverse these grounds for rejection and submit that the Action has not set forth a *prima facie* case showing that the subject matter of the instant claims, *i.e.*, polynucleotides encoding a Dual Specificity Phosphatase-14 (DSP-14) polypeptide, compositions comprising the DSP-14 encoding polynucleotides, and a method for expressing a DSP-14 polypeptide, lacks utility. Applicants' invention is directed in pertinent part to an isolated polynucleotide that encodes a DSP-14 polypeptide comprising all or a portion of the amino acid sequence set forth in SEQ ID NO:2, or a variant thereof that differs in one or more amino acid deletions, additions, insertions or substitutions at no more than 25% of the residues in SEQ ID NO:2, such that the polypeptide retains the ability to dephosphorylate an activated MAP-kinase; and to related compositions and methods. In certain embodiments, the invention is directed in pertinent part to an isolated polynucleotide that encodes at least fifteen consecutive amino acids of a polypeptide having a sequence corresponding to SEQ ID NO:2; to an antisense polynucleotide comprising at least 15 consecutive nucleotides complementary to a polynucleotide encoding a DSP-14 polypeptide; and to a polynucleotide that detectably hybridizes to the complement of the sequence recited in SEQ ID NO:1 under moderately stringent conditions that include a wash in 0.1X SSC and 0.1% SDS at 50 °C for 15 minutes; and to related compositions.

Applicants submit that the claimed invention has a well-established utility because a person having skill in the art would readily appreciate that the subject invention DSP-14 polynucleotide sequences encode a novel, full-length dual specificity phosphatase (or portions thereof), which is a polypeptide that is useful for understanding the regulation of dual specificity phosphatases within MAP-kinase cascades. Applicants further submit, as elaborated below, that the presently claimed DSP-14 encoding polynucleotides, and their use in the claimed method for producing a DSP-14 polypeptide, have (i) a utility that is specific to the claimed DSP-14 polynucleotide and to the method for producing the DSP-14 polypeptide; (ii) a substantial utility, in that the polynucleotides encode a useful protein that may be produced by the claimed method; and (iii) a credible utility, in that a person having ordinary skill in the relevant art would readily

appreciate that the polynucleotide encoding a novel DSP-14 polypeptide may be isolated, identified, and used in the method as claimed for producing the polypeptide.

Applicants respectfully submit that a person having ordinary skill in the art will immediately appreciate the usefulness of the invention based on its characteristics, which are described in the specification and recited in the claims of the present application. Applicants submit that given the instant disclosure and the state of the art, it is clear that dual specificity protein tyrosine phosphatases dephosphorylate both (i) phosphotyrosine and (ii) phosphothreonine and/or phosphoserine residues (*see, e.g.*, specification, page 2, lines 5-12, and references cited therein; page 6, line 25 through page 7, line 3) on specific substrates such as activated MAP-kinases, the regulation of which is important to the operation and control of conserved cellular signal transduction pathways (*see, e.g.*, specification page 1, line 22 through page 2, line 4). Prior to the present invention, regulation of signal transduction has remained poorly understood, in part because few dual specificity phosphatases have been identified (*see, e.g.*, specification, page 2, lines 12-20).

The presently claimed polynucleotides (*e.g.*, SEQ ID NO:1) encode polypeptides containing a protein tyrosine phosphatase active site motif (*see, e.g.*, specification, page 13, lines 1-2) that is conserved in dual specificity phosphatases (*see, e.g.*, specification, page 46, lines 8-14, and references cited therein). Furthermore, the full-length DSP-14 polypeptides (*e.g.*, SEQ ID NO:2) encoded by the invention polynucleotides show significant homology to other MAP-kinase phosphatases (*see, e.g.*, specification, page 13, lines 7-8; Figure 3). On the basis of the identified active site motif and the homology of the encoded DSP-14 polypeptides with other dual specificity phosphatase family members, a person having ordinary skill in the art would reasonably believe that the DSP-14 polypeptide described in the instant specification has the *specific* ability to dephosphorylate an activated MAP-kinase. Therefore, such a person having skill in the art would readily understand that utility of the disclosed invention resides in furthering the understanding of the role of dual specificity phosphatases in MAP-kinase cascades that mediate cellular transduction of biological signals.

Applicants further submit that the claimed DSP-14 polynucleotide and its dual specificity phosphatase polypeptide products have a specific and substantial utility that a person having ordinary skill in the art would find credible. On the basis of the identified active site

motif and the homology of the encoded DSP-14 polypeptide to other dual specificity phosphatase family members, a person having ordinary skill in the art would readily appreciate that the claimed polynucleotides have the specific and particular use of encoding a useful polypeptide, DSP-14. Uses of the claimed DSP-14 encoding polynucleotide and its expression to produce DSP-14 polypeptide translation products include, for example, dephosphorylation of a tyrosine- or a serine-/threonine-phosphorylated phosphoprotein substrate, such as an activated MAP-kinase (*see, e.g.,* specification, page 40, lines 15-26); generation of DSP-14 variants to be tested for phosphoprotein phosphatase activity (*see, e.g.*, specification, page 18, line 21 through page 19, line 24); identification of agents that alter intracellular molecular signaling by modulating DSP-14 activity (*see, e.g.*, specification, page 37, line 7 through page 40, line 12); and detection of DSP-14 expression in biological samples (*see, e.g.*, specification, page 33, line 25 through page 37, line 4). The claimed DSP-14 polynucleotides also may find use as probes, primers, or antisense oligonucleotides. (*See, e.g.*, specification, page 10, lines 3-13). In addition, applicants submit that the claimed method of producing the DSP-14 polypeptide is specific to the disclosed DSP-14 polynucleotide sequence (*see also, e.g.*, specification, page 9, line 8 through page 10, line 2).

Applicants respectfully disagree with the assertion found in the Action that given the prior art, a person skilled in the art would not believe that a DSP-14 polypeptide encoded by the claimed polynucleotides has credible utility. Applicants submit that, on the contrary, the references cited by the Examiner *support* a specific, substantial, and credible utility for applicants' invention. The Examiner cites U.S. Patent No. 6,258,582 ('582, Acton), asserting that a protein tyrosine phosphatase disclosed in '582 has a different enzymatic activity than that of the DSP-14 polypeptide encoded by the isolated polynucleotides of the instant claims. Applicants traverse this assertion in the Action and submit that the definition of what is a protein tyrosine phosphatase as disclosed in '582 is consistent with, and not contradictory to, the teachings of the present application, even where the subject invention polynucleotides encode a structurally distinct phosphatase.

As noted above, uses of the presently claimed DSP-14 encoding polynucleotides to express DSP-14 polypeptides also include, for example, dephosphorylation of a tyrosine- or a serine-/threonine-phosphorylated phosphoprotein substrate, such as an activated MAP-kinase

(*see, e.g.,* specification, page 40, lines 15-26); or generation of DSP-14 variants to be tested for phosphoprotein phosphatase activity (*see, e.g.*, specification, page 18, line 21 through page 19, line 24). Similarly, a protein tyrosine phosphatase (PTP) as defined in '582 includes a protein or polypeptide that is capable of facilitating (*e.g.,* catalyzing) the removal of a phosphate group "attached to a tyrosine, serine or threonine residue" of a protein or polypeptide substrate (column 9, lines 52-61). Further according to the teachings of '582, protein tyrosine phosphatases with such a specificity include dual specificity phosphatases ('582, column 9, lines 57-61). In other words, dual specificity phosphatases are members of the PTP family (*e.g.*, present specification at page 46, lines 9-14), such that the assertion in the Action (page 5, lines 17*ff*) that "dual specificity phosphatases belong to a family of enzymes which catalyze the hydrolyses of many phosphorylated proteins" is equally applicable to dual specificity phosphatases of the instant application (*i.e.*, DSP-14) and to structurally homologous dual specificity phosphatases of '582. Given the teachings of the present application, a person skilled in the art would therefore have little reason to doubt that DSP-14 possesses dual specificity phosphatase activity.

Additionally, the phosphatase (HHLM-4, SEQ ID NO:4) disclosed in U.S. Patent No. 6,132,964 ('964) (Bandman et al.) and referred to by the Examiner also "has chemical and structural homology with human dual-specificity protein phosphatase(s)" ('964, column 13, lines 29-31; see also column 13, lines 1-22). For example, HHLM-4 ('964, SEQ ID NO:4) contains the conserved dual specificity phosphatase PTP catalytic domain motif (-C-X_5-R-, instant specification at page 46, lines 9-12) that is present in DSP-14 (*e.g.*, instant application, Fig. 2 and SEQ ID NO:2). Applicants therefore traverse the allegation in the Action that prior art sequences, which have homology to the DSP-14 sequence of the instant invention, also have activities that are unrelated to the enzymatic activities of DSP-14. By contrast, and for reasons given above, applicants submit that a person skilled in the art would note that both sequences include the conserved PTP active site motif and so would reasonably believe that these similar sequences have similar activities. Thus, two patents cited in the Action ('582 and '964) disclose other members of the dual specificity phosphatase family that are structurally distinct from the DSP-14 dual specificity phosphatase encoded by the subject invention polynucleotides, but which phosphatases are functionally related by virtue of the specific ability to dephosphorylate a phosphoprotein substrate. The '582 and '964 patents do, however, articulate the need in the art

to identify new protein tyrosine phosphatases because these enzymes are important modulators in cellular activities. (*See* both '582 and '964, Background of the Invention).

As noted above, the Examiner also cites a third patent, U.S. Patent No. 6,268,135 (the '135 patent, '135) (Acton), asserting that the patent teaches a phospholipase (SEQ ID NO: 2 of '135) that has 40% homology to SEQ ID NO:2 of the present invention, and asserting further that residues 133-166 of SEQ ID NO: 2 ('135) share an even greater percentage sequence homology with the amino acid sequence encompassing the DSP-14 tyrosine phosphatase active site domain of the present application (residues 143-175 of SEQ ID NO: 2). In particular, the Examiner alleges that the present invention lacks credible utility where SEQ ID NO:2 of the instant application and SEQ ID NO:2 of '135 exhibit high homology but have different utility and function (*e.g.*, phospholipase activity for SEQ ID NO:2 of '135 and dual specificity phosphatase activity for SEQ ID NO:2 of the present application).

Applicants traverse this portion of the utility rejection in view of Acton ('135) and respectfully point out that Acton ('135) nowhere demonstrates that the polypeptide set forth in SEQ ID NO:2 of Acton ('135) possesses phospholipase activity, nor for that matter does any polypeptide disclosed and claimed in Acton ('135) exhibit phospholipase activity. The Action cites '135 as authority for disclosure and claims directed to a polypeptide having phospholipase activity, but the Action fails to provide any evidence or reasoning in support of such a position.

Applicants respectfully submit that a careful reading of Acton ('135) reveals a great deal of background information about phospholipases in general, but that '135 fails to disclose and claim any polypeptide that exhibits demonstrable phospholipase activity and that comprises a sequence having high homology to SEQ ID NO:2 of the present application. The '135 patent discloses that a phospholipase A_2 active site includes the consensus sequence CCX_2HX_2C ('135, at column 7, lines 60-65). The '135 patent further teaches that the cardiovascular system associated phospholipase (CSAPL) polypeptide disclosed therein and having the sequence set forth in SEQ ID NO:2 of the '135 patent possesses a phospholipase A_2 active site located at amino acid positions 131-138 of that sequence (column 8, lines 3-6). Applicants are puzzled by these assertions in the Action, and respectfully note that amino acids 131-138 of SEQ ID NO:2 of '135 (QGRVLVHC) fail to conform to the phospholipase A_2 active site consensus sequence (CCX_2HX_2C), nor does any portion of SEQ ID NO:2 of '135 include the

phospholipase A_2 active site motif. Combined with the observation that Acton ('135) fails to demonstrate that the polypeptide of SEQ ID NO:2 is capable of phospholipase A_2 catalytic activity, applicants believe that the assertion in the Action that '135 teaches phospholipase A_2 activity in a dual specificity phosphatase-like polypeptide must be called into question. By contrast, the PTP catalytic site motif (-C-X_5-R-, instant specification at page 46, lines 8-14; see also Keyes, *Biochim. Biophys. Acta* 1265:152-60; '582, at column 13, lines 4-18; '694 at column 13, lines 21-40 and SEQ ID NO:4 therein), which is present at positions 147-153 of SEQ ID NO:2 of the present application, can also be found at positions 138-144 of SEQ ID NO:2 of the '135 patent, and Acton recognizes that this portion of the CSAPL polypeptide ('135 SEQ ID NO:2) falls within a region having sequence homology to a known dual specificity phosphatase ('135, at column 56, lines 19-29). Applicants therefore respectfully submit that Acton ('135) fails to show that SEQ ID NO:2 therein possesses phospholipase A_2 structure or activity, and further that if anything, a person having ordinary skill in the art would find more credible that SEQ ID NO:2 of Acton is a dual specificity phosphatase than that this polypeptide could be a phospholipase.

Therefore, applicants submit that in view of the cited art, persons skilled in the art would find quite credible that the polynucleotides of the present invention encode a novel, full-length DSP-14 polypeptide belonging to the dual specificity phosphatase family.

Applicants further submit that the isolated polynucleotide of the present invention has a substantial utility with a real-world application, in that the subject invention polynucleotide encodes a novel, dual specificity phosphatase that plays a role in regulation of a MAP-kinase signal transduction cascade. As disclosed in the specification, persons having ordinary skill in the art would readily appreciate that MAP-kinases are components of conserved cellular signal transduction pathways (*see, e.g.*, specification, page 1, line 22 through page 2, line 4). Skilled artisans would also know that MAP-kinases are activated by phosphorylation at a dual phosphorylation motif, which is required for kinase activity, and that MAP-kinases are inactivated through dephosphorylation by dual specificity phosphatases (*see, e.g.*, specification, page 1, lines 24-29). The physiological role of MAP-kinase signaling has been correlated with cellular events, such as proliferation, oncogenesis, development, and differentiation (*see, e.g.*, specification, page 1, line 29 through page 2, line 4). Therefore, the expression and activity of

dual specificity phosphatases are significant to the regulation of these MAP-kinase-mediated cellular functions.

Applicants also submit that providing the polynucleotide sequence for a DSP-14 polypeptide has the real-world and practical use, for example, of enabling a person skilled in the art to detect DSP-14 expression and phosphatase activity, and to identify modulators of this activity (see generally specification, pages 33-40). For instance, a substantial and real-world use for the claimed polynucleotides and related products is assessment of the patterns of DSP-14 polynucleotide and/or polypeptide expression in particular cells or tissues, which permits a person having skill in the art to diagnose a proliferative disorder (*see, e.g.*, specification at page 36, line 27 through page 37, line 4) or to determine which tissue or cell type would be an appropriate source for establishing a primary cell culture or for establishing a genetically engineered cell line, such as may be useful to create a biological disease model (*see, e.g.*, specification page 34, lines 3-18).

Additionally, applicants submit that a person having ordinary skill in the art would readily appreciate that disclosure in the instant application of a new member of the expanding dual specificity phosphatase family contributes to the understanding of dual specificity phosphatase regulation of MAP-kinases, and therefore facilitates development of methods for diagnosis and treatment of conditions associated with MAP-kinase cascades. Applicants thus respectfully submit that the present invention has a well-established utility that is specific, substantial, and credible, in full compliance with all requirements of 35 U.S.C. § 101, and hence request that the rejection be withdrawn.

Moreover, and with regard to enablement, applicants respectfully traverse the rejection under 35 U.S.C. § 112, first paragraph, and submit that the instant specification provides sufficient disclosure to teach a person having ordinary skill in the art how to make and use the claimed invention. As noted above, the invention is directed in pertinent part to an isolated polynucleotide that encodes a DSP-14 polypeptide comprising all or a portion of the amino acid sequence set forth in SEQ ID NO:2, or a variant thereof, and to related compositions and methods, including a method of producing a DSP-14 polypeptide. As disclosed in the specification and recited in the claims, according to certain embodiments the subject invention

polynucleotide encodes a DSP-14 polypeptide that retains the ability to dephosphorylate an activated MAP-kinase.

Applicants submit that the present application teaches a person having ordinary skill in the art how to make and use the claimed polynucleotides and their expression products without undue experimentation. For example, the specification describes the sequence of a DSP-14 encoding polynucleotide (SEQ ID NO:1), which may be used to design oligonucleotides for use as primers or probes for detection and/or isolation of a polynucleotide encoding a DSP-14 polypeptide (*see, e.g.*, specification, page 10, lines 7-8; page 11, line 27 through page 12, line 4). Such oligonucleotides can further be identified using methods known in the art and disclosed in the instant specification, such as computer algorithms, for example, Align or BLAST (*see, e.g.*, specification, page 10, lines 14-27). DSP-14 polypeptides may be expressed and isolated, and DSP-14 phosphatase activity assayed, according to methods known in the art and disclosed in the specification (*see, e.g.*, page 9, line 8 through page 10, line 2; page 18, line 2 through page 19, line 24). The specification further teaches how to evaluate patterns of gene expression when evaluating agents that modulate DSP-14 activity (*e.g.*, page 39, lines 3-10). Applicants submit that all of the aforementioned methods may be performed by permissible routine screening and without undue experimentation.

Accordingly, applicants respectfully submit that the claimed invention has a well-established utility that is specific, substantial, and credible, and which therefore satisfies the requirements of 35 U.S.C. § 101. Applicants further submit that the specification enables a person having ordinary skill in the art to make and use the claimed invention in full compliance with 35 U.S.C. § 112, first paragraph. Therefore, applicants respectfully request that the rejection of claims 2-14 be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 2-5 and 11-13 under 35 U.S.C. § 112, first paragraph, asserting that the claims are directed to subject matter that is not adequately described in the specification. In particular, the Examiner alleges that the specification describes only a single representative species of the claimed genus. The Examiner further asserts that no relationship between the structure and function of that single species is disclosed.

Applicants respectfully traverse this ground for rejection and submit that applicants possessed the claimed invention, as disclosed in the present specification and recited in the instant claims, at the time the application was filed. Applicants' invention is directed to an isolated polynucleotide that encodes at least 15 consecutive amino acids of a polypeptide having a sequence corresponding to SEQ ID NO:2, and to related compositions. In certain embodiments, the invention is directed to an isolated polynucleotide that detectably hybridizes to the complement of the sequence recited in SEQ ID NO:1 under moderately stringent conditions that include a wash in 0.1X SSC and 0.1% SDS at 50 °C for 15 minutes, and to related compositions.

Applicants respectfully submit that the instant specification reasonably conveys sufficient, detailed, and relevant characteristics of the claimed polynucleotides, and that a person skilled in the art would recognize that applicants possessed the claimed invention at the time the application was filed. Applicants submit that by disclosing a polynucleotide sequence (SEQ ID NO:1) encoding a novel, full-length DSP-14 polypeptide (SEQ ID NO:2), applicants have presented a detailed structural chemical formula from which a skilled person may make and use the polynucleotides as claimed. Contrary to the assertion in the Action, the instant specification provides additional relevant and identifying characteristics of the claimed polynucleotides by disclosing the relationship between functional activity, that is, dual specificity phosphatase activity, and the structure of the DSP-14 polypeptide encoded by the claimed polynucleotide. Dual specificity phosphatases belong to the larger family of protein tyrosine phosphatases that share a conserved catalytic domain containing a cysteine residue situated N-terminal to a stretch of five variable amino acids followed by an arginine residue. (*See* specification, page 46, lines 8-13 and references cited therein.) The instant application discloses the sequence and location of the catalytic active site of the DSP-14 polypeptide, thus explicitly teaching the relationship between the structure and function of DSP-14. (*See, e.g.,* specification, page 12, line 28 through page 13, line 2).

Applicants submit that the specific and detailed description of a polynucleotide encoding a DSP-14 polypeptide, or variant thereof, provides sufficiently detailed and relevant identifying characteristics of species within the genus. The specification discloses that a DSP-14 polynucleotide is any polynucleotide that encodes at least a portion of a DSP-14 polypeptide or a

variant thereof, or that is complementary to such a polynucleotide and that comprises preferably at least 30 consecutive nucleotides, which would encode a polypeptide of at least 10 amino acids. (*See, e.g.*, specification, page 10, lines 3-13). The specification also teaches that certain polynucleotides encode a DSP-14 polypeptide and that other polynucleotides may find use as probes, primers, or antisense oligonucleotides. (*See, e.g.*, specification, page 10, lines 7-8). Applicants submit that polynucleotide sequences useful as probes, primers, or antisense oligonucleotides are intended to be partial DNA sequences and therein find their use. Furthermore, polynucleotides useful for such purposes are those species that are apparent to a person of ordinary skill in the art from the disclosed polynucleotide sequence, SEQ ID NO:1.

Applicants further submit that disclosure of the complete chemical structure of a polynucleotide encoding a DSP-14 polypeptide, or variant thereof, provides sufficiently detailed and relevant identifying characteristics of a polynucleotide that detectably hybridizes to the complement of the sequence recited in SEQ ID NO:1 under moderately stringent conditions that include a wash in 0.1X SSC and 0.1% SDS at 50 °C for 15 minutes. As noted above, a DSP-14 polynucleotide is any polynucleotide that encodes at least a portion of a DSP-14 polypeptide or a variant thereof, or that is complementary to such a polynucleotide, which includes polynucleotides useful as primers and probes. (*See, e.g.,* specification, page 10, lines 3-10.) As is well known in the art, the ability of a polynucleotide to hybridize to a complementary nucleic acid molecule depends on the chemical properties of the nucleic acids involved, which are determined by the nucleotide sequences of such molecules. As disclosed in the instant specification, polynucleotides substantially homologous to a naturally occurring DNA or RNA that encodes a native DSP-14 polypeptide are capable of hybridizing to a disclosed DSP-14 encoding sequence such as SEQ ID NO:1 under moderately stringent conditions. (*See, e.g.*, specification, page 10, line 27 through page 11, line 14). Additional stringency is provided by a wash in 0.1X SSC and 0.1% SDS at 50 °C for 15 minutes. (*See, e.g.*, specification, page 11, lines 4-6). Applicants therefore submit that the specification provides a detailed description of relevant and identifying characteristics of the claimed genus that reasonably conveys to a person skilled in the art that applicants possessed more than a single representative species.

In view of the above remarks and the present amendment, applicants respectfully submit that the subject matter claimed is adequately described by the specification such that a

person skilled in the art would recognize that applicants possessed the claimed invention at the time the application was filed. Applicants therefore submit that the instant application complies with the written description requirements under 35 U.S.C. §112, first paragraph, and respectfully request that the rejection of the claims be withdrawn.

The Examiner rejected claims 2-14 under 35 U.S.C. §112, first paragraph, alleging that the specification does not enable a person skilled in the art to make and use the claimed invention. More specifically, the Examiner asserts that the disclosure is not commensurate with the scope of the invention as claimed, in that the specification does not enable a polynucleotide encoding a DSP-14 polypeptide that has 50% identity with SEQ ID NO:2. In particular, the Examiner asserts that the specification does not provide enabling support for determining the enzymatic, functional, and biological activity of the polypeptide disclosed in SEQ ID NO:2 and also fails to disclose how to use the polypeptide. The Examiner further asserts that the art is unpredictable, and that searching for an analog sharing 50% sequence homology with the polypeptide disclosed in SEQ ID NO:2 and having a desired function would require undue experimentation.

Applicants respectfully traverse these grounds for rejection and submit that the specification enables a person skilled in the art to make and use the invention as claimed. As noted above, applicants' invention is directed in pertinent part to an isolated polynucleotide that encodes a DSP-14 polypeptide comprising all or a portion of the amino acid sequence set forth in SEQ ID NO:2, or a variant thereof that differs in one or more amino acid deletions, additions, insertions or substitutions at no more than 25% of the residues in SEQ ID NO:2, such that the polypeptide retains the ability to dephosphorylate an activated MAP-kinase; and to related compositions and methods. In certain embodiments the invention is directed in pertinent part to an isolated polynucleotide that encodes at least 15 consecutive amino acids of a polypeptide having a sequence corresponding to SEQ ID NO:2; to an antisense polynucleotide comprising at least 15 consecutive nucleotides complementary to a polynucleotide encoding a DSP-14 polypeptide; and to a polynucleotide that detectably hybridizes to the complement of the sequence recited in SEQ ID NO:1 under the recited conditions; and to related compositions.

Applicants respectfully submit that the instant specification provides explicit guidance enabling a skilled artisan to make and use the claimed polynucleotides without undue experimentation. Applicants submit that the specification describes how to make and use an isolated polynucleotide that encodes a polypeptide having the sequence of DSP-14 recited in SEQ ID NO:2, or a variant thereof that differs in one or more amino acid deletions, additions, insertions or substitutions at no more than 25% of the residues in SEQ ID NO:2, such that the polypeptide retains the ability to dephosphorylate an activated MAP-kinase. The specification discloses the polynucleotide sequence (SEQ ID NO:1) that encodes a DSP-14 polypeptide (see SEQ ID NO:2). By using computer algorithms well known in the art and disclosed in the specification, such as Align or the BLAST algorithm, a person skilled in the art can determine the percentage of sequence identity of a polynucleotide to the disclosed DSP-14 polynucleotide sequence. (*See, e.g.,* specification page 10, lines 14-27). Such a polynucleotide may encode a DSP-14 polypeptide, which is capable of dephosphorylating a DSP-14 substrate, including activated (*i.e.*, phosphorylated) MAP-kinases (*see, e.g.,* specification, page 6, line 25 through page 7, line 3). As disclosed in the specification and known in the art, MAP-kinases are components of conserved cellular signal transduction pathways, and MAP kinase signaling has been correlated with cellular events such as proliferation, oncogenesis, development, and differentiation. (*See, e.g.,* specification page 1, line 22 through page 2, line 4.)

To identify whether a polynucleotide as recited in the claims would encode a polypeptide that is capable of exhibiting phosphatase activity, the specification explicitly teaches that the DSP-14 active site comprises the sequence, VHCVMGRSRSATLVLAYLM (SEQ ID NO:3). (*See, e.g.,* specification page 8, lines 24-25; page 13, lines 1-2; SEQ ID NO:2 at amino acid positions 145-163). Applicants submit that given the sequence and the location of the amino acids comprising the active site, a person having skill in the art, using the alignment methods as discussed above, can readily identify whether a polynucleotide will encode the active site of a DSP-14 polypeptide.

Furthermore, the ability of a DSP-14 polypeptide product to dephosphorylate a DSP-14 substrate may be evaluated according to methods known in the art and disclosed in the specification without undue experimentation. (*See, e.g.,* specification page 18, line 1 through page 19, line 24). A person having skill in the art can identify such a DSP-14 polynucleotide by

expressing the polynucleotides (*see, e.g.,* specification, pages 33-37). The polypeptides expressed can then be analyzed for their ability to dephosphorylate a suitable substrate, such as an activated MAP-kinase, according to assays for detecting DSP-14 activity, which are also described in the specification (*see, e.g.,* specification, page 18, line 1 through page 19, line 24). Furthermore, a person skilled in the art can identify or make a DSP-14 polypeptide variant that differs in one or more amino acid deletions, insertions, or substitutions at no more than 25% of the residues in SEQ ID NO:2 and that retains the ability to dephosphorylate a DSP-14 substrate. (*See, e.g.,* specification, page 6, line 25 through page 7, line 3; page 8, line 6 through page 9, line 7). A variant DSP-14 polypeptide product of a DSP-14 encoding polynucleotide has the ability to dephosphorylate tyrosine and threonine/serine residues that is not substantially diminished relative to that of a native DSP-14 polypeptide. (*See, e.g.,* specification page 6, lines 25-29). Applicants respectfully submit that given the teachings of the present specification and, *inter alia*, the level of skill in the art, performing such assays to determine whether an encoded polypeptide has DSP-14 phosphatase activity would not amount to undue experimentation, but instead is merely a matter of permissible routine screening. (*In re Wands*, 858 F.2d 731, 736, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation such as routine screening.").

Applicants further submit that the specification not only provides enabling disclosure for a person having skill in the art to make and use a DSP-14 polynucleotide that encodes a polypeptide, but also to make and use DSP-14 polynucleotides as probes, primers, or antisense oligonucleotides. (*See, e.g.,* specification, page 10, lines 3-13). Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides. (*See, e.g.,* specification, page 10, lines 5-7). Such DSP-14 polynucleotides may be designed and made by using the sequence set forth in SEQ ID NO:1, or a portion thereof. These sequence-specific primers may be used as primers to amplify cDNA prepared from cells or tissues, or may be used to isolate a full-length gene from a suitable library. (*See, e.g.,* specification, page 11, line 21 through page 12, line 4).

A polynucleotide that is complementary to at least a portion of a coding sequence, such as an antisense polynucleotide, may also be used as a probe or a primer, or to modulate gene expression. (*See, e.g.,* specification, page 13, line 19-21). Applicants submit that the instant

specification enables a person having skill in the art to make and use an antisense polynucleotide comprising at least 15 consecutive nucleotides complementary to an isolated polynucleotide that encodes a polypeptide having the sequence of DSP-14 recited in SEQ ID NO:2, or a variant thereof that differs in one or more amino acid deletions, additions, insertions or substitutions at no more than 25% of the residues in SEQ ID NO:2, such that the polypeptide retains the ability to dephosphorylate an activated MAP-kinase. Applicants further submit that in view of the high percentage of identical residues shared by SEQ ID NO:2 and such a variant, making and using such an antisense oligonucleotide would not require undue experimentation.

Applicants submit that a person skilled in the art is enabled to make and use an isolated polynucleotide that detectably hybridizes to the complement of the sequence set forth in SEQ ID NO:1 under moderately stringent conditions that include a wash in 0.1X SSC and 0.1% SDS at 50 °C for 15 minutes. As disclosed in the specification and known to persons skilled in the art, the addition of the recited wash step in a hybridization procedure provides additional stringency. (*See, e.g.,* specification, page 11, lines 1-6). Variations in stringency or hybridization conditions may be achieved by altering any one or more of time, temperature, and concentration of solution components that are used for prehybridization, hybridization, and wash steps. (*See, e.g.,* specification, page 11, lines 6-14). Applicants submit that selection of suitably stringent conditions for hybridization by a person skilled in the art does not require undue experimentation but is a matter of permissible routine screening.

In view of the above remarks and the present amendment, applicants submit that the specification enables a person having skill in the art to make and use related compositions, such as the expression vectors of claims 4, 8, and 12; the host cells of claims 5, 9, and 13; and the method of claim 14. The specification teaches that an expression vector may be constructed and introduced into a host cell by transfection or transformation according to methods known in the art and disclosed in the specification. (*See, e.g.*, specification, page 15, line 19 through page 17, line 14). Furthermore, a DSP-14 polypeptide may be produced by culturing a host cell, prepared as described above, and isolating the DSP-14 polypeptide from the host cell culture according to the method recited in claim 14 and described in the specification (*see, e.g.,* page 17, lines 20-26). The specification further discloses, in detail, methods for detecting expression of a DSP-14 polypeptide. (*See, e.g.,* specification, page 33, line 25 through page 37, line 4). Applicants

submit that on the basis of the disclosure in the specification and methods well known in the molecular biology art, persons skilled in the art can make and use the aforementioned compositions and methods readily and without undue experimentation.

Accordingly, applicants respectfully submit that the present application satisfies all the requirements of 35 U.S.C. § 112, first paragraph, and therefore request that the rejection of the claims be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claim 10 under 35 U.S.C. § 112, second paragraph, for indefiniteness. More specifically, the Examiner asserts that claim 10 encompasses embodiments directed to nucleic acid sequences for which no structure or function is disclosed.

Applicants respectfully traverse this ground for rejection and submit that in view of the present amendment, claim 10 complies with the requirements of 35 U.S.C. § 112, second paragraph. The invention is directed in pertinent part to an antisense polynucleotide comprising at least 15 consecutive nucleotides complementary to a polynucleotide that encodes a polypeptide comprising the sequence of DSP-14 set forth in SEQ ID NO:2, or a variant thereof that differs in one or more amino acid deletions, additions, insertions or substitutions at no more than 25% of the residues in SEQ ID NO:2, such that the polypeptide retains the ability to dephosphorylate an activated MAP-kinase.

Applicants submit that the instant claim defines the subject matter with sufficient clarity and precision to apprise a person skilled in the art of the scope of the claim. The claim particularly points to an antisense polynucleotide that has a *structure* defined by the nucleotide sequence of a DSP-14 polynucleotide that encodes a DSP-14 polypeptide having the sequence set forth in SEQ ID NO: 2, or that encodes a variant with a high degree of homology (*e.g.*, greater than 75%) to SEQ ID NO:2. Furthermore, the claimed subject matter is directed to an antisense polynucleotide that comprises at least 15 consecutive nucleotides complementary to a polynucleotide that encodes a DSP-14 polypeptide, wherein the polynucleotide has the *function* of an *antisense* polynucleotide (see specification, page 14, lines 6-28), while the encoded polypeptide, the expression of which may be altered by such an antisense polynucleotide, has the *function* of dephosphorylating an activated MAP-kinase. Therefore, applicants submit that claim

10 as presently recited particularly points out and distinctly claims subject matter that applicants regard as their invention, and thus complies with the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore respectfully request that the rejection of the claim be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

The Examiner rejected claim 2 under 35 U.S.C. § 103 for alleged obviousness over Acton (U.S. Patent No. 6,258,582). The Examiner asserts that it would have been obvious for a person having ordinary skill in the art to obtain the claimed invention by using a 12-amino acid sequence (amino acids 114-125 of SEQ ID NO:5, which are identical to amino acids 152-163 of SEQ ID NO: 2 of the present invention) disclosed by Acton, and allegedly taught by Acton to be conserved among all phosphatases, to prepare a nucleic acid probe to screen for phosphatases in human and other organisms' genomic or cDNA libraries.

Applicants respectfully submit that the present amendment canceling claim 2 obviates the grounds for this rejection and renders rejection of claim 2 moot. Applicants further note that Acton fails to teach or suggest the subject matter of claim 3, directed to an isolated polynucleotide that encodes at least 15 consecutive amino acids of a polypeptide having a sequence corresponding to SEQ ID NO:2. Applicants submit that the Acton reference does not provide any motivation or suggestion to modify the reference to achieve applicants' invention. Acton does not teach or suggest that by probing a genomic or cDNA library with a polynucleotide that encodes the polypeptide SRSATLVLAYLM would a person having ordinary skill in the art successfully obtain the polynucleotide of the instant claim. Applicants further submit that the claimed polynucleotide cannot be made obvious simply because a person of ordinary skill in the art may have been capable of using the sequence disclosed by Acton and using methods known in the art at the time the application was filed to search for *any* dual specificity phosphatase. *See In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) (ruling that a "general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of the search"). Applicants submit that only with impermissible hindsight could a person having ordinary skill in the art reconstruct the claimed invention.

Furthermore, applicants submit that the Acton reference does not provide a teaching, suggestion, or motivation that a person having ordinary skill in the art would achieve applicants' invention with a reasonable expectation of success. Contrary to the assertion in the Action, Acton does not teach that the peptide 12-mer, SRSATLVLAYLM, is a conserved sequence among all phosphatases but merely discloses that *"[p]referably*, the phosphatase extended catalytic active domain includes the following amino acid consensus sequence (VXVHCXAGXSRSXTX(3)AYLM, X = any amino acid)" (column 12, lines 35-38) (emphasis added), which is a sequence of 21 amino acids with 7 variant amino acids. Even assuming *arguendo*, that a person having ordinary skill in the art would be motivated to use the SRSATLVLAYLM 12-mer sequence of Acton to arrive at the subject invention polynucleotide encoding DSP-14, applicants submit that such a person could not do so with any *reasonable* expectation of success. Specifically, the skilled person would have to generate oligonucleotides that represented all of the myriad possible codon combinations that are theoretically capable of encoding the desired sequence in order to specifically amplify SEQ ID NO:1 of the present invention. Due to the well known degeneracy of the genetic code, each of the 20 naturally occurring amino acids may be encoded by up to six nucleotide triplet codons. A person having ordinary skill in the art would therefore readily appreciate that practically an infinite number of distinct DNA sequences can encode the 12 amino acid sequence disclosed by Acton. Therefore, applicants submit that Acton fails to provide any *reasonable* expectation of success in arriving at the present invention, because generating oligonucleotides that represent all of these possible codon arrangements would be both impractical and impossible.

Applicants further submit that a skilled person would have had no *a priori* motivation to look for, nor any *a priori* expectation of arriving at, a novel dual specificity phosphatase having the specific properties of DSP-14 as disclosed in the present application and recited in the instant claims. DSP-14 is a newly discovered member of the expanding family of structurally homologous dual specificity phosphatases that are characterized by distinct substrate specificities (*e.g.*, MAP kinase) and subcellular localizations, and diverse patterns of tissue expression (see Muda et al., *J. Biol. Chem.* 272:5141 (1997), abstract). In particular, of numerous possible dual specificity phosphatase-encoding sequences that may be encoded in a source genome or cDNA library (or, for example, that might be specifically amplified by PCR as

a consequence of which particular oligonucleotide primers a skilled artisan might select from the myriad of possible combinations that can be designed from the available prior art sequences), nothing in the prior art would have pointed the skilled artisan to the presently claimed DSP-14 sequences *per se*. Moreover, the Examiner has not pointed to any teaching or suggestion in the art that would lead an artisan to arrive at the subject invention DSP-14 to the exclusion of other possible dual specificity phosphatases. As noted above, Acton teaches that a phosphatase consensus sequence of 21 amino acids contains 7 variant amino acids, four of which are in the portion of the consensus sequence encompassing the cited 12-mer. Applicants therefore submit that a person skilled in the art using a polynucleotide encoding the polypeptide SRSATLVLAYLM to probe a genomic or a cDNA library would expect to obtain the polynucleotide sequence disclosed by Acton, not the polynucleotide sequence of the claimed invention.

Applicants are puzzled by the Examiner's reference to phospholipases being useful enzymes and do not understand how that assertion allegedly renders applicants' invention obvious when neither the cited Acton reference (U.S. Patent No. 6,258,582) nor the present application relate to, or disclose, phospholipases. Phospholipases are enzymes that hydrolyze ester bonds of plasma membrane-bound phospholipids and triglycerides. The present application discloses a novel dual specificity protein tyrosine phosphatase DSP-14, which is a protein phosphatase that dephosphorylates both phosphotyrosine and phosphothreonine/serine residues (*see, e.g.,* specification, page 2, lines 5-12, and references cited therein).

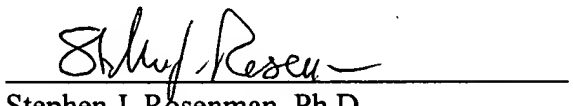
Applicants further submit that the differences between the amino acid sequences of the polypeptides encoded by the claimed invention polynucleotides and the amino acid sequences of the cited art also show that the cited art does not teach or suggest all the claim limitations of the instant invention. Specifically, Acton does not teach or suggest 15 consecutive amino acids of a polypeptide having the sequence set forth in SEQ ID NO: 2. Applicants therefore respectfully submit that the claims of the instant application satisfy the requirements for nonobviousness under 35 U.S.C. § 103.

All of the claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Ralf M. Luche and Bo Wei

SEED Intellectual Property Law Group PLLC



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 28 of page 12 and continuing through page 13, line 8, has been amended as follows:

A cDNA sequence encoding DSP-14 is provided in Figure 1 (SEQ ID NO:1), and the predicted amino acid sequence is provided in Figure 2 (SEQ ID NO:2). The DSP-14 active site VHCVMGRSRSATLVLAYLM (SEQ ID NO:3), is located at positions 145 through 163 of SEQ ID NO:2. Sequence information immediately adjacent to this site was used to design 5' and 3' RACE reactions with human testis cDNA to identify a 1165 base pair cDNA that corresponds to a mRNA that displays a higher abundance in brain, testis, kidney and skeletal muscle RNA. This cDNA encodes a protein of 220 amino acids that is referred to herein as dual specificity phosphatase-~~6~~14, or DSP-14. DSP-14 shows significant homology to other MAP-kinase phosphatases, as shown by the sequence comparison presented in Figure 3.

In the Claims:

Claim 2 has been canceled.

Claims 4, 6, and 11 have been amended as follows:

2. (Cancelled) An isolated polynucleotide that encodes at least ten consecutive amino acids of a polypeptide having a sequence corresponding to SEQ ID NO:2.

3. An isolated polynucleotide that encodes at least fifteen consecutive amino acids of a polypeptide having a sequence corresponding to SEQ ID NO:2.

4. (Amended) An expression vector comprising a polynucleotide according to claim ~~2 or~~ 3.

5. A host cell transformed or transfected with an expression vector according to claim 4.

6. (Amended) An isolated polynucleotide that encodes a polypeptide comprising the sequence of DSP-14 set forth in SEQ ID NO:2, or a variant thereof that differs in one or more amino acid deletions, additions, insertions or substitutions at no more than 25% of the residues in SEQ ID NO:2, such that the polypeptide retains the ability to dephosphorylate an activated MAP-kinase~~according to claim 1~~.

7. A polynucleotide according to claim 6, comprising the sequence recited in SEQ ID NO:1.

8. An expression vector comprising a polynucleotide according to claim 6.

9. A host cell transformed or transfected with an expression vector according to claim 8.

10. An antisense polynucleotide comprising at least 15 consecutive nucleotides complementary to a polynucleotide according to claim 6.

11. (Amended) An isolated polynucleotide that detectably hybridizes to the complement of the sequence recited in SEQ ID NO:1 under moderately stringent conditions that include a wash in 0.1X SSC and 0.1% SDS at 50 °C for 15 minutes.

12. An expression vector comprising a polynucleotide according to claim 10 or claim 11.

13. A host cell transformed or transfected with an expression vector according to claim 12.

14. A method of producing a DSP-14 polypeptide, comprising the steps of:

(a) culturing a host cell according to claim 9 under conditions that permit expression of the DSP-14 polypeptide; and

(b) isolating DSP-14 polypeptide from the host cell culture.